Cochrane Library

Cochrane Database of Systematic Reviews

Prophylactic antibiotics for preventing pneumococcal infection in children with sickle cell disease (Review)

Rankine-Mullings AE, Owusu-Ofori S

Rankine-Mullings AE, Owusu-Ofori S.
Prophylactic antibiotics for preventing pneumococcal infection in children with sickle cell disease.
Cochrane Database of Systematic Reviews 2017, Issue 10. Art. No.: CD003427.
DOI: 10.1002/14651858.CD003427.pub4.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Review]

Prophylactic antibiotics for preventing pneumococcal infection in children with sickle cell disease

Angela E Rankine-Mullings[1], Shirley Owusu-Ofori[2]

[1]Sickle Cell Unit, Caribbean Institute for Health Research, University of the West Indies, Kingston, Jamaica. [2]Transfusion Medicine Unit, Komfo Anokye Teaching Hospital, Kumasi, Ghana

Contact address: Angela E Rankine-Mullings, Sickle Cell Unit, Caribbean Institute for Health Research, University of the West Indies, Kingston, Jamaica. angela.rankinemullings@uwimona.edu.jm.

Editorial group: Cochrane Cystic Fibrosis and Genetic Disorders Group.
Publication status and date: Edited (no change to conclusions), published in Issue 3, 2020.

Citation: Rankine-Mullings AE, Owusu-Ofori S. Prophylactic antibiotics for preventing pneumococcal infection in children with sickle cell disease. *Cochrane Database of Systematic Reviews* 2017, Issue 10. Art. No.: CD003427. DOI: 10.1002/14651858.CD003427.pub4.

ABSTRACT

Background

Persons with sickle cell disease (SCD) are particularly susceptible to infection. Infants and very young children are especially vulnerable. The 'Co-operative Study of Sickle Cell Disease' observed an incidence rate for pneumococcal septicaemia of 10 per 100 person years in children under the age of three years. Vaccines, including customary pneumococcal vaccines, may be of limited use in this age group. Therefore, prophylactic penicillin regimens may be advisable for this population. This is an update of a Cochrane Review first published in 2002, and previously updated, most recently in 2014.

Objectives

To assess the effects of antibiotic prophylaxis against pneumococcus in children with SCD in relation to:

1. incidence of infection;

2. mortality;

3. drug-related adverse events (as reported in the included studies) to the individual and the community;

4. the impact of discontinuing at various ages on incidence of infection and mortality.

Search methods

We searched the Cochrane Cystic Fibrosis and Genetic Disorders Group Haemoglobinopathies Trials Register, which is comprised of references identified from comprehensive electronic database searches and also two clinical trials registries: ClinicalTrials.gov and the WHO International Registry Platform. Additionally, we carried out handsearching of relevant journals and abstract books of conference proceedings.

Date of the most recent search: 19 December 2016.

Selection criteria

All randomised or quasi-randomised controlled trials comparing prophylactic antibiotics to prevent pneumococcal infection in children with SCD with placebo, no treatment or a comparator drug.

Data collection and analysis

Both authors independently extracted data and assessed trial quality. The authors used the GRADE criteria to assess the quality of the evidence.

Main results

Five trials were identified by the searches, of which three trials (880 children randomised) met the inclusion criteria. All of the included trials showed a reduced incidence of infection in children with SCD (SS or Sβ0Thal) receiving prophylactic penicillin. In trials which investigated initiation of penicillin on risk of pneumococcal infection, the odds ratio was 0.37 (95% confidence interval 0.16 to 0.86) (two trials, 457 children) (low-quality evidence), while for withdrawal the odds ratio was 0.49 (95% confidence interval 0.09 to 2.71) (one trial, 400 children) (low-quality evidence). Adverse drug effects were rare and minor. Rates of pneumococcal infection were found to be relatively low in children over the age of five.

Overall, the quality of the evidence for all outcomes was judged to be low. The results from the risk of bias assessment undertaken identified two domains in which the risk of bias was considered to be high, these were incomplete outcome data (attrition bias) (two trials) and allocation concealment (selection bias) (one trial). Domains considered to have a low risk of bias for all three trials were selective reporting (reporting bias) and blinding (performance and detection bias).

Authors' conclusions

The evidence examined suggests that prophylactic penicillin significantly reduces risk of pneumococcal infection in children with homozygous SCD, and is associated with minimal adverse reactions. Further research may help to determine the ideal age to safely withdraw penicillin.

PLAIN LANGUAGE SUMMARY

Regular antibiotics for preventing pneumococcal infection in young children with sickle cell disease

Review question

We reviewed the evidence about the effects of prophylactic antibiotic regimens for preventing pneumococcal infection in children with sickle cell disease (SCD). This is an updated version of a previously published Cochrane Review.

Background

People living with SCD are especially prone to respiratory and blood infections. These infections are often caused by a germ (bacteria) known as *Streptococcus pneumoniae,* otherwise known as pneumococcus, which can cause many types of serious illnesses. Individuals with SCD can get infections more easily than unaffected persons because their spleen (organ that filters blood) does not work correctly, and also because damaged tissue and bone resulting from SCD can harbour bacteria. Infection prevention is therefore one of the major ways to improve the health of persons living with SCD and reduce the risk of death. The highest risk of infection occurs in children under three years old, but the special vaccines that help to prevent illnesses with *Streptococcus pneumoniae* are of limited use in this young population. Therefore, regular antibiotics in addition to these special vaccines are needed to prevent infection. As risk of infection decreases with age, there might be a time when preventative antibiotic treatment can be discontinued.

Search date

The evidence is current to 19 December 2016.

Study characteristics

We gathered evidence for this Cochrane Review by examining three clinical trials with over 800 children included.

Key results and quality of the evidence

All three clinical trials showed a reduced rate of pneumococcal infection in children with SCD receiving penicillin preventatively. Two of these trials looked at whether treatment was effective. The third trial followed on from one of the early trials and looked at when it was safe to stop treatment. Adverse drug effects were rare and minor. However, there were problems with children keeping to the treatment schedule and with the development of antibiotic resistance. The quality of the evidence for both primary and secondary outcomes (end result) was judged to be low.

We conclude that penicillin given preventatively reduces the rate of pneumococcal infections in children with SCD under five years of age. The risk of infection in older children is lower, and the follow-on trial did not show a significant increase in risk when regular penicillin was halted at five years old. Further research is needed to look at how commonly bacteria develop that are resistant to treatment and how clinically important this is.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Summary of findings - initiation of penicillin prophylaxis versus placebo

Penicillin prophylaxis compared with placebo for pneumococcal infection in SCD

Patient or population: children with SCD

Settings: outpatients

Intervention: initiation of penicillin prophylaxis

Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	placebo	penicillin				
Incidence of *S pneumoniae* infection Isolated bacterial infection Follow-up: up to 5 years	90 per 1000	33 per 1000 (14 to 77)	OR 0.37 (95% CI 0.16 to 0.86)	457 (2)	⊕⊕⊖⊖ **low[1,2]**	The John trial reported that no pneumococcal isolations had occurred while the children were actually receiving penicillin. However, this was stopped after the participants reached age 3 years and was not continued for the 5-year duration of the trial.
Deaths Follow-up: up to 5 years	40 per 1000	4 per 1000 (0.4 to 84)	OR 0.11 (95% CI 0.01 to 2.11)	457 (2)	⊕⊕⊖⊖ **low[1,2]**	One of the trials reported no deaths in either group for the duration of the prophylaxis (John 1984). In addition, one child in the placebo group died as a result of fulminant *H influenzae*, OR 0.11 (95% CI 0.01 to 2.11) (PROPS 1986).
Adverse effects Follow-up: up to 5 years	See comment	See comment	N/A	457 (2)	⊕⊕⊖⊖ **low[1,2]**	No adverse effects were seen in the John trial after penicillin injections (John 1984). The penicillin was well-tolerated and no confirmed allergic reactions occurred in the PROPS trial (PROPS 1986).
Antibiotic-resistant organisms isolated	Outcome not reported				N/A	

Follow-up: N/A					
Requirement of other courses of antibiotics Follow-up: N/A	Outcome not reported			N/A	
Compliance to treatment Follow-up: average 15 months	See comment	See comment	N/A	215 (1)	⊕⊕⊝⊝ **low**[2,3]	An attempt was made to measure compliance via pill counts and urine analysis, but only 66% of appointments were kept and only 31% of the expected numbers of urine samples were obtained (PROPS 1986). The John trial did not measure compliance but attempted to minimise non-compliance by giving monthly injections.

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; ***H influenzae***: *Haemophilus influenzae*; **N/A**: not applicable; **OR**: odds ratio; **SCD**: sickle cell disease; ***Spneumoniae***:*Streptococcus pneumoniae*

GRADE Working Group grades of evidence
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

1. Downgraded once for risk of bias as the randomisation methodology was unclear in one of the trials and both trials were at risk of bias due to incomplete outcome data.
2. Downgraded once due to imprecision as there were low event rates.
3. Downgraded once due to risk of bias from incomplete outcome data.

Summary of findings 2. Summary of findings - withdrawal of penicillin prophylaxis versus continuation

Penicillin prophylaxis compared with placebo for pneumococcal infection in SCD

Patient or population: children with SCD who have been receiving prophylactic penicillin for at least two years

Settings: outpatients

Intervention: penicillin prophylaxis

Comparison: placebo (withdrawal of penicillin prophylaxis)

Outcomes	Illustrative comparative risks* (95% CI)	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments

	Assumed risk	Corresponding risk				
	Control (placebo)	Penicillin prophylaxis				
Incidence of *S pneumoniae* Confirmed bacterial infection Follow-up: average 3.2 years	20 per 1000	10 per 1000 (2 to 54)	OR 0.49 (95% CI 0.09 to 2.71)	400 (1)	⊕⊕⊖⊖ **low[1,2]**	
Deaths Follow-up: average 3.2 years	See comment	See comment	N/A	400 (1)	⊕⊕⊖⊖ **low[1,2]**	No deaths were associated directly with infection, but there were two fatalities in the penicillin group due to acute sickle chest syndrome, and two in the placebo group due to stroke, OR 0.99 (95% CI 0.14 to 7.10).
Adverse effects: incidences of nausea and vomiting Follow-up: average 3.2 years	5 per 1000	10 per 1000 (1 to 111)	OR 1.99 (95% CI 0.18 to 22.12)	400 (1)	⊕⊕⊖⊖ **low[1,2]**	
Antibiotic-resistant organisms isolated Follow-up: average 3.2 years	See comment	See comment	N/A	400 (1)	⊕⊕⊖⊖ **low[1,2]**	Antibiotic-resistant organisms were identified although this was not analysed as an outcome of the trial. There was a non-significant increased likelihood of children in the penicillin group to carry multiple-drug resistant pneumococci compared to the control group.
Requirement of other courses of antibiotics Follow-up: average 3.2 years	840 per 1000	790 per 1000 (462 to 1000)	OR 0.94 (95% CI 0.55 to 1.61)	400 (1)	⊕⊕⊖⊖ **low[1,2]**	
Compliance to treatment Follow-up: N/A	Outcome not reported				N/A	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **N/A**: not applicable; **OR**: odds ratio; **SCD**: sickle cell disease; ***Spneumoniae***:*Streptococcus pneumoniae*

GRADE Working Group grades of evidence
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

---

1. Downgraded once due to risk of bias from unclear allocation concealment and incomplete outcome assessment.
2. Downgraded once due to imprecision from low event rates.

BACKGROUND

Description of the condition

Sickle cell disease (SCD) is a genetic haemoglobin disorder, caused by inheritance from both parents of an altered beta-globin chain gene. The abnormal haemoglobin within red blood cells causes them to deform when they give up oxygen. These dense, sickle shaped cells are easily destroyed, leading to haemolytic anaemia, thus oxygen carriage is reduced. They can also adhere to the lining of the blood vessels, which results in tissue and organ damage leading to complications, such as severe pain crises, stroke and splenic infarction. Approximately 60,000 African-Americans, 10,000 persons in the UK and one in 60 persons in West Africa now suffer from the disease (Davies 1997; Hickman 1999). Globally, there are 250,000 new births with SCD per year. Despite improved care and services for people with SCD in developed countries, the average life expectancy for men and women with homozygous disease (SS) is 42 years and 48 years respectively (Platt 1994). Infection is the major cause of death in children under the age of three years (Leikin 1989).

Persons living with SCD are particularly susceptible to infection, most commonly infections of the respiratory tract and septicaemia (Serjeant 2001). This is partly due to splenic dysfunction, which reduces the ability of the immune system to clear circulating antigens. In addition, abnormalities have been suggested in components of the immune system such as complement, immunoglobulins, leucocyte function and cell-mediated immunity, further disabling the response to infection (Serjeant 2001). Tissue damage and bone necrosis may also harbour infectious agents. These abnormalities result in an increased risk of encapsulated bacterial infections such as pneumococcus, and an increase in *Haemophilus influenzae* (*H influenzae*), *Neiserria meningitidis*, *Staphylococcus aureus* and *Escherischia coli* septicaemias (Serjeant 2001).

There are different forms of SCD, depending on inheritance of various mutated genes which result in differing types of haemoglobin genotypes. If the S gene is inherited from both parents the child will have homozygous SCD (SS), whereas inheritance from one parent in combination with a different altered beta-globin chain gene can lead to many other forms of the disease. The most common are haemoglobin SC disease (SC), haemoglobin S-beta thalassaemia zero (Sβ0Thal) and haemoglobin S-beta thalassaemia plus (Sβ+Thal). People with each of these diseases are affected to different extents with the symptoms of SCD, but susceptibility to infection is most apparent with SS and Sβ0Thal.

Infection occurs in persons with SCD from infancy, with the highest risk before the age of three years, and significantly lower risk in older children and adults (Robinson 1966; Zarkowsky 1986). Although comprehensive vaccination programmes are in place in developed countries, some vaccines, in particular the customary pneumococcal vaccines (unconjugated polysaccharide capsular antigen), are of limited use in children less than three years old due to suboptimal antibody responses. While it has been noted that early diagnosis and treatment of SCD has decreased mortality and morbidity rates in recent years (Lee 1995), the 'Co-operative Study of Sickle Cell Disease' (Leikin 1989; Zarkowsky 1986) observed that from 1980 to 1981 the incidence of pneumococcal septicaemia in children under three years old was 10 per 100 patient years, with a 30% fatality rate. Approximately 4.5% of the children in the trial experienced at least one episode of bacteremia (Zarkowsky 1986). As a result of the vulnerability of children to pneumococcal infection, an effective prophylactic antibiotic regimen is needed.

Description of the intervention

Possible regimens to prevent pneumococcal infection involve daily oral use or monthly intramuscular injections of penicillin. Compliance with prophylactic antibiotics is poor in many areas (Berkovitch 1998; Cummins 1991) and resistance (pneumococcal) could occur through prolonged or intermittent use of broad-spectrum antibiotics (Chesney 1992), potentially resulting in greater morbidity and mortality. Penicillins can also result in hypersensitivity reactions including, rarely, anaphylaxis and encephalopathy, which can be fatal (BNF 2001). However, serious adverse drug reactions are unusual.

As children get older they have a reduced risk of pneumococcal infection (Lobel 1982; Robinson 1966). Therefore, there is a possibility that a prophylactic regimen could be modified or stopped later in childhood.

Why it is important to do this review

The purpose of this review was to determine if prophylactic antibiotics are effective in preventing pneumococcal infection. In addition we aimed to explore if there is an appropriate age when treatment can be safely withdrawn, without increasing the risk of infection. We also examined whether there are any potential adverse effects of long-term prophylaxis on the individual or in the community. This is an updated version of a previously published Cochrane Review (Hirst 2002; Hirst 2012).

OBJECTIVES

To assess the effects of antibiotic prophylaxis against pneumococcus in children with SCD in relation to:

1. incidence of infection;
2. mortality;
3. drug related adverse events (as reported in the included studies) to the individual and the community;
4. the impact of discontinuing at various ages on incidence of infection and mortality.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised or quasi-randomised clinical trials (published or unpublished). Trials that use cluster randomisation were included provided the groups were similar at baseline.

Types of participants

Children under the age of 16 years with homozygous SCD (SS), sickle beta thalassaemia (Sβ0Thal and Sβ+Thal) and sickle haemoglobin C disease (SC), proven by electrophoresis, with family studies or DNA tests as appropriate, of either sex and in any setting.

Types of interventions

Prophylactic antibiotics compared to placebo, no treatment or a comparator treatment.

Types of outcome measures

Primary outcomes

1. Number of participants developing *Streptococcus pneumoniae* (*S pneumoniae*) infection, confirmed with cultures
2. Deaths

Secondary outcomes

1. Adverse drug effects
2. Antibiotic-resistant organisms isolated
3. Requirement for other courses of antibiotics
4. Compliance with antibiotic prophylaxis, measured by counting doses and urine samples

Search methods for identification of studies

There were no restrictions regarding language or publication status.

Electronic searches

Relevant trials were identified from the Group's Haemoglobinopathies Trials Register using the terms: (sickle cell OR (haemoglobinopathies AND general) AND antibiotics AND prophylaxis.

The haemoglobinopathies register is compiled from electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL) (updated each new issue of the Cochrane Library) and weekly searches of MEDLINE. Unpublished work is identified by searching the abstract books of five major conferences: the European Haematology Association conference; the American Society of Hematology conference; the British Society for Haematology Annual Scientific Meeting; the Caribbean Health Research Council Meetings; and the National Sickle Cell Disease Program Annual Meeting. For full details of all searching activities for the register, please see the relevant section of the Cochrane Cystic Fibrosis and Genetic Disorders Group's website.

Date of the most recent search of the Group's Haemoglobinopathies Trials Register: 19 December 2016.

We also searched the online trial registries: ClinicalTrials.gov (www.ClinicalTrials.gov); and the the WHO International Clinical Trials Registry Platform (ICTRP) (http://www.who.int/ictrp/en/) (Appendix 1).

Searching other resources

The bibliographic references of all retrieved literature were reviewed for additional reports of trials.

Data collection and analysis

Selection of studies

Two authors (AR-M (previously CH) and SO) independently selected the trials to be included in the review. If disagreement arose on the suitability of a trial for inclusion in the review, a consensus was reached by discussion.

Data extraction and management

Two authors (AR-M (previously CH) and SO) independently extracted the data (using standard data acquisition forms) from the included trials.

Assessment of risk of bias in included studies

The authors performed an assessment of all RCTs using the Cochrane 'risk of bias' tool, according to chapter eight of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). The two review authors worked independently to assess each element of potential bias listed below as 'high', 'low' or 'unclear' risk of bias. We reported a brief description of the judgement statements upon which the authors have assessed potential bias in the 'Characteristics of included studies' table. We ensured that a consensus on the degree of risk of bias was met through comparing the review authors' statements. We reported on the following domains.

- Selection bias (random sequence generation and allocation concealment)
- Performance bias (blinding of participants and personnel)
- Detection bias (blinding of outcome assessment)
- Attrition bias (incomplete outcome data)
- Reporting bias (selective reporting)
- Other bias

Measures of treatment effect

We recorded outcomes as dichotomous event counts, e.g. present or absent. We aimed to calculate a pooled estimate of the treatment effect for each outcome across trials (for binary outcomes the odds of an outcome among treatment allocated participants to the corresponding odds among controls). We analysed trials comparing antibiotic prophylaxis with placebo or no treatment separately from those comparing different antibiotic agents, doses and routes of administration.

Continuous data, such as organ function tests, would have been recorded as either mean change from baseline for each group or mean post treatment values and standard deviation for each group, and a pooled estimate of the treatment effect for each outcome across trials calculated.

Dealing with missing data

We would have sought full reports from authors, had trials been found published in abstract form, presented at meetings or reported to the authors. We contacted the primary investigators of the John trial and requested that they confirm the numbers of participants allocated to each trial group, as this is unclear in the original trial report (John 1984).

We also contacted the authors of PROPS (PROPS 1986) and PROPS II (PROPS II 1995) to request information on overlap of participants between trials, since it would be inappropriate to aggregate data if this would result in counting participants in meta-analysis more than once. The authors confirmed that a significant proportion of participants were not involved in both trials (less than 10%).

In order to allow intention-to-treat analysis, irrespective of later exclusion (regardless of cause) or loss to follow-up, we collected data by allocated treatment groups.

Assessment of heterogeneity

For future versions of this review if more trials are included and more meta-analyses possible, we plan to investigate any heterogeneity identified between trials. We plan to assess the degree of statistical heterogeneity between studies using the I^2 statistic (Higgins 2003). This measure describes the percentage of total variation across studies that are caused by heterogeneity rather than by chance (Higgins 2003). The values of I^2 lie between 0% and 100%, and a simplified categorisation of heterogeneity that the review authors used is of low (I^2 value of less than 25%), moderate (I^2 value of between 25 and 50%), and high (I^2 value of over 50%) (Higgins 2003).

Subgroup analysis and investigation of heterogeneity

If adequate numbers of trials had been included, we would have performed subgroup analysis for type of sickle cell disease if appropriate. We planned to analyse children with SS and Sβ0Thal separately from those with SC and Sβ+Thal. None of the latter groups of participants, however, had been included in the trials, possibly because they are not as susceptible to overwhelming infection, particularly with *S. pneumoniae*.

We analysed trials which assessed initiation or withdrawal of treatment separately, as we felt that such trials address different clinical questions.

Sensitivity analysis

If adequate numbers of quasi-randomised trials had been included, we would also have performed a sensitivity analysis.

RESULTS

Description of studies

Summary details are given in the 'Characteristics of included studies' section.

Five trials (880 randomised children) were found of which three met the predefined inclusion criteria (John 1984; PROPS 1986; PROPS II 1995).

In one trial, 265 children with homozygous sickle cell disease were recruited from outpatient clinics of the University Hospital of the West Indies, and 23 subsequently withdrew (John 1984). Children with a previous history of pneumococcal infection or splenectomy were excluded. Children were aged between six months and 36 months at recruitment. They were randomised into one of four groups, to receive monthly intramuscular penicillin injections or nothing, plus either pneumococcal vaccine or *H influenzae* type B vaccine. Penicillin prophylaxis was withdrawn at the age of three years, as the authors thought that older children might not be compliant to the painful injections, although these participants were still analysed in the groups to which they had been assigned. The trial lasted for five years. A misprint in the primary publication made treatment group numbers difficult to establish, as the numbers given do not add up to the trial cohort. However, the authors were contacted and the numbers confirmed (37 in the group receiving *H influenzae* type B vaccine alone, rather than 27 as printed).

The 'Prophylaxis with Oral Penicillin in Children with Sickle Cell Anaemia' clinical trial was a multicentre, randomized, double-blind, placebo- controlled clinical trial. A total of 215 children with homozygous SCD from the USA were randomised to receive oral prophylactic penicillin, 125 mg twice daily, or placebo (PROPS 1986). They were aged between three months and 36 months at the start of the trial, and all had pneumococcal vaccination at one and two years of age. Children were excluded from the trial if they were receiving long-term transfusion therapy or antibiotics, or if they were allergic to penicillin. The trial was terminated eight months earlier than scheduled, after the occurrence of 15 cases of pneumococcal septicaemia, 13 in the placebo group and two in the penicillin group, showing an 84% reduction in pneumococcal septicaemia with penicillin prophylaxis (P = 0.0025).

A further trial in the USA by the same group, aimed to evaluate the consequences of discontinuing penicillin prophylaxis in children with SS or Sβ0 sickle cell disease at the age of five years (PROPS II 1995). A small proportion of children was involved in both PROPS and PROPS II (PROPS 1986; PROPS II 1995). Children with a previous history of pneumococcal infection or splenectomy were excluded. A total of 400 children were randomised to either continue on penicillin prophylaxis, or have it replaced with an identical placebo, to determine the incidence of pneumococcal infection on stopping penicillin at age five years. The children were all around five years old (mean 5.1 years) and had been taking penicillin prophylactically for at least two years. All children had received pneumococcal vaccination within the 12 months preceding the start of the trial.

Results of the search

Summary details are given in the 'Characteristics of included studies' section.

Five trials, potentially eligible for inclusion were identified (Berkovitch 1998; John 1984; Lewthwaite 1962; PROPS 1986; PROPS II 1995).

Included studies

Three trials were eligible for inclusion (John 1984; PROPS 1986; PROPS II 1995).

In one trial, 265 children with homozygous sickle cell disease were recruited from outpatient clinics of the University Hospital of the West Indies, and 23 subsequently withdrew (John 1984). Children with a previous history of pneumococcal infection or splenectomy were excluded. Children were aged between six months and 36 months at recruitment. They were randomised into one of four groups, to receive monthly intramuscular penicillin injections or nothing, plus either pneumococcal vaccine or *H influenzae* type B vaccine. Penicillin prophylaxis was withdrawn at the age of three years, as the authors thought that older children might not be compliant to the painful injections, although these participants were still analysed in the groups to which they had been assigned. The trial lasted for five years. A misprint in the primary publication made treatment group numbers difficult to establish, as the numbers given do not add up to the trial cohort. However, the authors were contacted and the numbers confirmed (37 in the group receiving *H influenzae* type B vaccine alone, rather than 27 as printed).

In the 'Prophylaxis with Oral Penicillin in Children with Sickle Cell Anaemia' trial, 215 SS children from the USA were randomised to receive oral prophylactic penicillin, 125 mg twice daily, or placebo (PROPS 1986). They were aged between three months

and 36 months at the start of the trial, and all had pneumococcal vaccination at one and two years of age. Children were excluded from the trial if they were receiving long-term transfusion therapy or antibiotics, or if they were allergic to penicillin. The trial was terminated eight months early, after the occurrence of 15 cases of pneumococcal septicaemia, 13 in the placebo group and two in the penicillin group, showing an 84% reduction in pneumococcal septicaemia with penicillin prophylaxis.

A further trial in the USA by the same group, aimed to evaluate the consequences of discontinuing penicillin prophylaxis in children with SS or Sβ0 sickle cell disease at the age of five years (PROPS II 1995). A small proportion of children was involved in both PROPS and PROPS II (PROPS 1986; PROPS II 1995). Children with a previous history of pneumococcal infection or splenectomy were excluded. A total of 400 children were randomised to either continue on penicillin prophylaxis, or have it replaced with an identical placebo, to determine the incidence of pneumococcal infection on stopping penicillin at age five years. The children were all around five years old (mean 5.1 years) and had been taking penicillin prophylactically for at least two years. All children had received pneumococcal vaccination within the 12 months preceding the start of the trial.

Excluded studies

Two trials were excluded from the review (Berkovitch 1998; Lewthwaite 1962). In one study all the participants received penicillin and were randomised to a 'compliance aid' or not (Berkovitch 1998). In the second study, alternate cases attending an outpatient clinic were given a subcutaneous injection of chloroquine and an intramuscular injection of penicillin. The control group received a subcutaneous injection of sterile water. The randomisation process was inadequate; of the 26 participants recruited only 13 were accounted for, outcomes were unclear and there was no mention of *S pneumoniae* (Lewthwaite 1962).

Risk of bias in included studies

It is critical to examine the quality of evidence provided by each included RCT. The risk of bias assessment has been expanded in this review update. Each specific type of bias is outlined and a judgement made. Evidence supporting the likelihood that a particular type of bias may be present is provided by referring to the particular area of text as was published. Additionally, for this update, a new domain of risk bias assessment has been added, this domain looks at selective reporting (reporting bias). Please refer to additional figures for a graphical representation of the risk of bias (Figure 1; Figure 2).

Figure 1. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

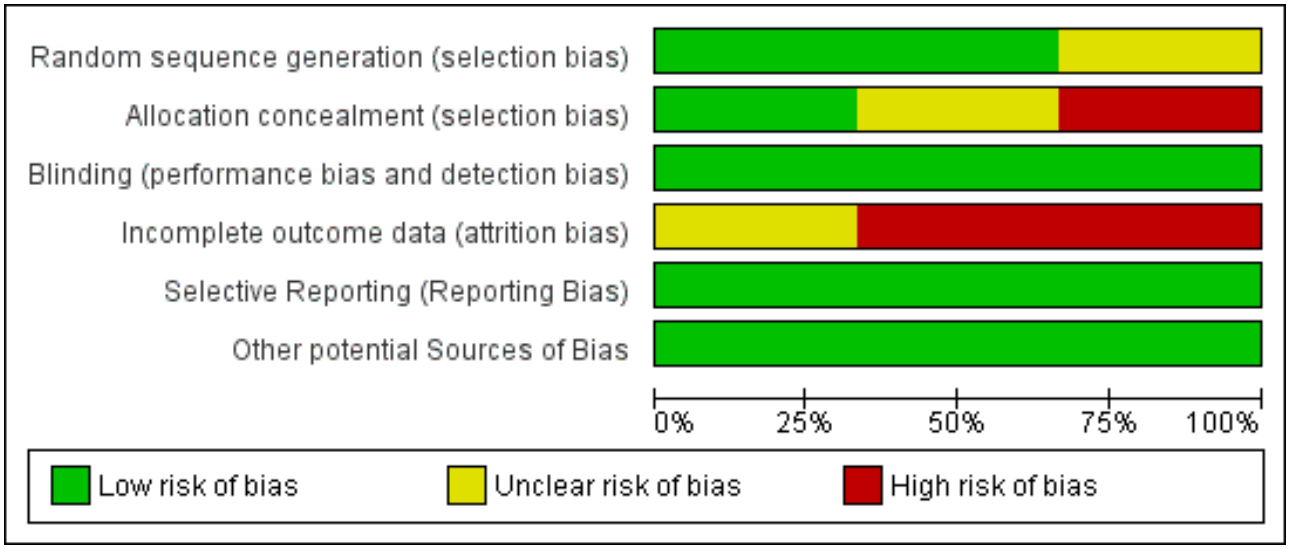
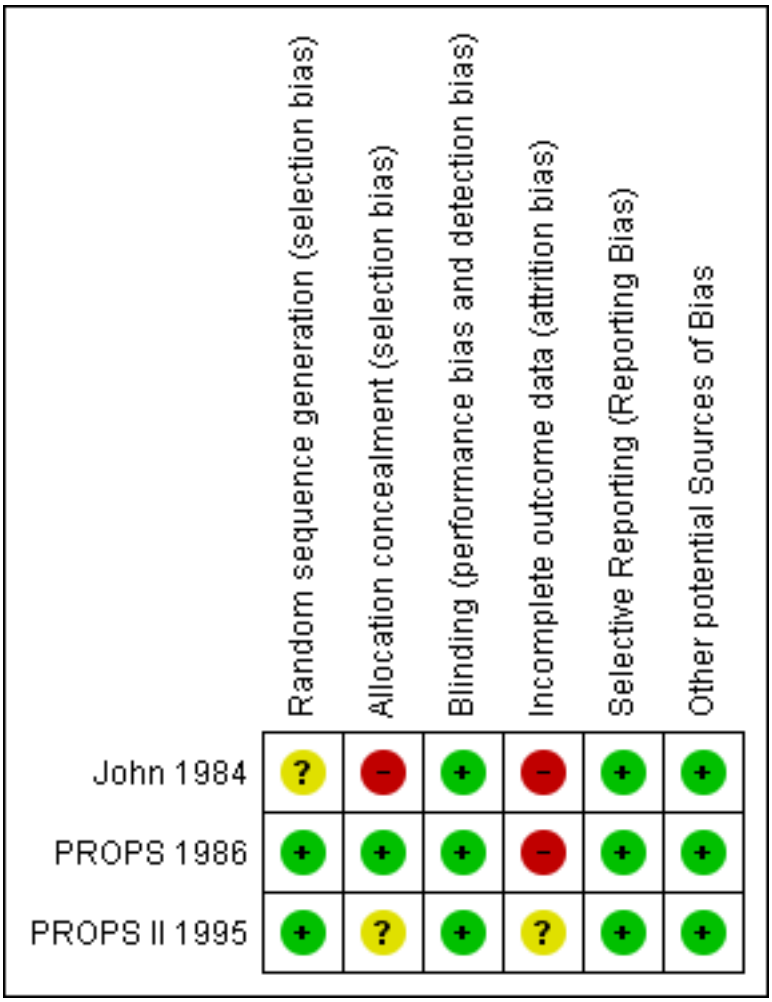


Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Random sequence generation

In the John trial, participants were randomised a total of 265 children were randomised to the four study groups. No details were given of the method of randomization (John 1984). We are therefore unable to fully assess the risk of selection bias. Therefore, the adequacy of sequence generation is classified as 'unclear risk'.

In the first PROPS trial, the PROPS data co-ordinating center generated the randomization numbers for each clinical site and with the help of the program office, directed patient - entry assignments by means of telephone contact. Sealed envelopes that were stored at the clinical centres were available as a back up for randomization when telephone contact was not possible, but they were rarely used. The randomization schedules were prepared with the use of blocked randomization within each clinic to ensure balance in numbers between two groups (PROPS 1986). The method of randomization is clearly stated hence this study is therefore considered to have a 'low risk' of bias for this domain.

In a further PROPS trial, randomisation was by permuted block method, stratified by clinical site and years of previous penicillin use (PROPS II 1995). The risk associated with the adequacy of random sequence generation was 'low risk'.

Allocation concealment

In the John trial, it was reported that the group allocation was changed due to the protocol for injected penicillin prophylaxis groups being inconvenient to some families who lived at remote addresses, or due to age of participants at recruitment so that the duration of penicillin treatment would have been too short to assess (John 1984). A total of 16 participants (6.6%) were therefore reassigned to groups which did not receive penicillin prophylaxis. The groups were uneven, with significantly more participants in the penicillin groups (143 in penicillin group compared to 99 in control group). We have therefore classified this as 'high risk' for this domain.

In the first PROPS study, a central co-ordinating centre directed participant entry assignment over the telephone (PROPS 1986). Sealed envelopes were also held at the clinical centres in case the central office could not be reached, to maintain allocation concealment. Therefore, we have assessed the risk of bias for allocation concealment as 'low risk'.

In a further PROPS trial, randomisation was by permuted block method, stratified by clinical site and years of previous penicillin use (PROPS II 1995). It was unclear whether allocation concealment

had been performed and we have therefore assessed this trial as having an 'unclear risk' of bias for this domain.

Blinding

The John trial was not blinded (John 1984). This clinical trial is considered to be at a low risk for performance bias as the lack of blinding is is not likely to affect outcome.

In the first PROPS trial, the participants and centre personnel were blinded to allocation, and placebo tablets looked almost identical to penicillin (PROPS 1986). Therefore, this trial is considered low risk for performance bias.

In the further PROPS trial identical placebo tablets were used to maintain double blinding of the participants and centre personnel, therefore, this trial was also considered to be at a low risk for performance bias (PROPS II 1995).

Incomplete outcome data

In the John trial, full baseline data for participant characteristics were not given (John 1984). "The trial was terminated prematurely in 25 children owing to splenectomy in 20, emigration in four, and the clinical decision to use prophylactic penicillin in one child with recurrent pneumococcal meningitis In these cases results up to the time of leaving the study were included in the analysis. There were seven deviations from the protocol caused by refusal to take penicillin after two and four injections (two), death before institution of randomised treatment (one), failure to treat with penicillin because of an error in age (one), inadvertent administration of penicillin to patients joining the study between 31 and 35 months of age (two), and removal to an inaccessible address, so that penicillin had to be stopped (one)." Aditionally, The study groups were also uneven with more participants in the penicillin group (143 in the penicillin group compared to 90 in the control group) and an "Intention to treat analysis was also undertaken" after participants were reassigned to protocol groups. Therefore, we have assessed the risk of bias due to attrition as 'high risk'.

In the 1986 PROPS trial, 219 participants were recruited from 23 centres throughout the USA (PROPS 1986). Four participants subsequently withdrew due to revisions of diagnosis, but 23 of these were subsequently withdrawn, mostly due to revision of genotype; these individuals had no severe infections and were not included in subsequent analyses. The trial was terminated early due to extreme results. There is therefore a possibility that the reported results may have been over-estimated and the risk of attrition bias was assessed as 'high risk'.

In the further PROPS trial, 400 participants were recruited from 18 centres in the USA (PROPS II 1995). The characteristics of participants in each group were similar at baseline. Four children died after randomisation, but other withdrawals are not reported, and it is unclear whether an intention-to-treat analysis was undertaken. The risk of attrition bias is therefore 'unclear'.

Selective reporting

The John trial was terminated prematurely in 25 children owing to splenectomy in 20, emigration in four, and the clinical decision to use prophylactic penicillin in one child with recurrent pneumococcal meningitis (see case 11; table III in the published trial article) (John 1984). In these cases results up to the time of leaving the study were included in the analysis. There were seven deviations from the protocol caused by refusal to take penicillin after two and four injections (two), death before institution of randomised treatment (one), failure to treat with penicillin because of an error in age (one), inadvertent administration of penicillin to patients joining the study between 31 and 35 months of age (two), and removal to an inaccessible address, so that penicillin had to be stopped (one). These cases were analysed according to their protocol." The outcomes of all subjects are adequately reported. The risk of selective reporting is considered to be low.

In the first PROPS trial both the primary and secondary outcomes were adequately reported "the trial was terminated earlier ....., after the occurrence of 15 episodes of pneumococcal sepsis 13 in the placebo group and 2 in the penicillin group" (PROPS 1986). Additionally baseline characteristics of both study groups are adequately reported.

In the further PROPS trial, "The primary end point was a comparison of the incidence of bacteremia or meningitis caused by *Streptococcus pneumoniae* in children continuing penicillin prophylaxis versus those receiving the placebo." Baseline characteristics and outcomes were adequately reported. The risk of reporting bias is therefore low (PROPS II 1995).

Summary of findings tables

In a post hoc change in line with current Cochrane guidance, at the 2017 update we added a summary of findings table for each comparison presented in the review. We selected the following six outcomes to report (chosen based on relevance to clinicians and consumers):

1. Number of participants developing *Streptococcus pneumoniae* (*S pneumoniae*) infection, confirmed with cultures
2. Deaths
3. Adverse drug effects
4. Antibiotic resistant organisms isolated
5. Requirement for other courses of antibiotics
6. Compliance with antibiotic prophylaxis, measured by counting doses and urine samples

We determined the quality of the evidence using the GRADE approach; and downgraded evidence in the presence of a high risk of bias in at least one study, indirectness of the evidence, unexplained heterogeneity or inconsistency, imprecision of results, high probability of publication bias. We downgraded evidence by one level if they considered the limitation to be serious and by two levels if very serious.

Other potential sources of bias

No other potential sources of bias were identified in these clinical trials that are thought to affect the outcome (low risk).

Effects of interventions

See: **Summary of findings for the main comparison** Summary of findings - initiation of penicillin prophylaxis versus placebo; **Summary of findings 2** Summary of findings - withdrawal of penicillin prophylaxis versus continuation

See Summary of findings for the main comparison and Summary of findings 2 for further details of quality of the evidence of each result.

Primary outcomes

1. Number of participants developing S pneumoniae infection, confirmed with cultures

Initiation of penicillin treatment versus placebo

In the trial by John, no pneumococcal events had occurred in children while they were receiving penicillin prophylaxis (John 1984). There was an overall incidence of six pneumococcal isolations in 99 participants (280 patient years at risk) in the placebo groups, compared to seven events in 143 participants (400 patient years at risk) in the penicillin groups (John 1984), odds ratio (OR) 0.80 (95% CI 0.26 to 2.45) (Analysis 1.1). However, all of these latter events occurred after the participants had stopped taking penicillin after their third birthday.

In the PROPS trial there were two cases of confirmed pneumococcal infection in 105 participants in the penicillin group compared to 13 of 110 in the placebo group (P = 0.0025, quoted from trial article), OR 0.14 (95% CI 0.03 to 0.66) (Analysis 1.1) (PROPS 1986).

Meta-analysis for these two trials, which addressed initiation of treatment, had an OR of 0.37 (95% CI 0.16 to 0.86) (low-quality evidence) (Analysis 1.1) showing a significant reduction of pneumococcal infection in those children treated with penicillin (John 1984; PROPS 1986).

Children in one of the trials also received either pneumococcal vaccination or *H influenzae* type B (Hib) vaccination (John 1984). Since the groups were unbalanced in numbers, differences in the infection rates between the vaccination groups could affect the results of analysis of penicillin versus no penicillin. However, analysis of infection rate in children receiving pneumococcal vaccination and HIB vaccination showed no statistical difference (test for subgroup differences: $Chi^2 = 0.36$, df = 1 (P = 0.55), $I^2 = 0\%$) (Analysis 1.2), therefore it does not seem that the imbalance of participants between these groups should affect the overall analysis of penicillin versus no penicillin.

Penicillin prophylaxis versus withdrawal of penicillin prophylaxis

In the PROPS II trial, which investigated withdrawal of penicillin prophylaxis compared to continuing, two events of pneumococcal infection occurred in the penicillin group, and four in the placebo group, OR 0.49 (95% CI 0.09 to 2.71) (low-quality evidence) (Analysis 1.1) (PROPS II 1995). In addition, there was a case of *H influenzae* in each group, a case of salmonella in the penicillin group, and two cases of group A beta-haemolytic streptococcus in the placebo group (PROPS II 1995). The difference between infection frequencies between the groups was therefore not statistically significant.

2. Deaths

Initiation of penicillin treatment versus placebo

In the trial by John, no deaths occurred after initiation of treatment (John 1984).

In the PROPS trial, there were no deaths due to pneumococcal infection in the penicillin group, but three in the control group (PROPS 1986). In addition, one child in the placebo group died as a result of fulminant *H influenzae*, OR 0.11 (95% CI 0.01 to 2.11) (low-quality evidence) (Analysis 1.3). Shortly after termination of the trial another child, from the penicillin group, also died from infection. Analysis of pneumococcal deaths only also has wide overall CIs, OR 0.15 (95% CI 0.01 to 2.85) (not shown in graph) (PROPS 1986).

Penicillin prophylaxis versus withdrawal of penicillin prophylaxis

In the PROPS II trial, no deaths were associated directly with infection, but there were two fatalities in the penicillin group due to acute sickle chest syndrome, and two in the placebo group due to stroke, OR 0.99 (95% CI 0.14 to 7.10) (low-quality evidence) (Analysis 1.3) (PROPS II 1995).

All results

No significant difference in number of deaths between participants treated with penicillin prophylaxis and those not treated is seen for either initiation or withdrawal of penicillin. The wide CIs in both trials indicate considerable uncertainty between a highly protective effect and a large increase in risk of death. This uncertainty reflects the small number of deaths in these two trials, and thus for more conclusive data on all causes of mortality larger or longer trials are required.

Secondary outcomes

1. Adverse drug effects

Initiation of penicillin treatment versus placebo

In the trial by John no adverse side effects were noted for the penicillin injections, although the vaccines, which were also given, caused some injection site reactions and fever (John 1984) (low-quality evidence). In the PROPS trial it is stated that the penicillin was well-tolerated and no confirmed allergic reactions occurred (PROPS 1986) (low-quality evidence).

Penicillin prophylaxis versus withdrawal of penicillin prophylaxis

In the PROPS II trial there were three recorded incidences of nausea and vomiting (one in the placebo group), and two localised reactions to vaccines (PROPS II 1995) (low quality evidence) (Analysis 1.4).

2. Antibiotic-resistant organisms isolated

Initiation of penicillin treatment versus placebo

This was not recorded in either the John or the first PROPS trials (John 1984; PROPS 1986).

Penicillin prophylaxis versus withdrawal of penicillin prophylaxis

In the PROPS II trial, antibiotic-resistant organisms were identified, although this was not analysed as an outcome of the trial (PROPS II 1995). However, within the PROPS II trial, an examination of a subset of the trial was carried out and 27% of the 226 participants were observed to carry *S pneumoniae* at some time, and in 9% at least one isolate of penicillin intermediate or resistant pneumococci was found (Woods 1997). There was no significant difference in incidence between groups, although there was a non-significant increased likelihood of children in the penicillin group to carry multiple-drug resistant pneumococci compared to the control group (low-quality evidence).

3. Requirement for other courses of antibiotics

Initiation of penicillin treatment versus placebo

This was not recorded in either the John or the first PROPS trials (John 1984; PROPS 1986).

Penicillin prophylaxis versus withdrawal of penicillin prophylaxis

In the PROPS II trial, 1155 additional courses of antibiotics were given in the penicillin group, and 1278 in the placebo group, in the treatment of febrile events (PROPS II 1995). In each group, 169 children were treated with at least one course of additional antibiotics, OR 0.94 (95% CI 95% 0.55 to 1.61) (low-quality evidence) (Analysis 1.5).

4. Compliance with antibiotic prophylaxis

Initiation of penicillin treatment versus placebo

In the John trial, penicillin was given as monthly intramuscular injections, to minimise non-compliance (John 1984). In the PROPS trial, an attempt was made to assess compliance through pill counts and urine analysis, but only 66% of appointments were kept and only 31% of the expected numbers of urine samples were obtained, making analysis meaningless (PROPS 1986).

Penicillin prophylaxis versus withdrawal of penicillin prophylaxis

The PROPS II trial gave no data regarding compliance (PROPS II 1995).

DISCUSSION

Summary of main results

The PROPS trial was a well-conducted trial, including 215 children with homozygous SCD (SS), and shows a significantly reduced risk of pneumococcal infection in those receiving prophylactic penicillin (PROPS 1986). Due to the early termination of the trial, there is a possibility that the reported results may have been over-estimated and the risk of attrition bias was assessed as 'high risk'. The results of the John trial appear to support these findings in a different population, than the West Indies, and using a different dose and route of administration, with no cases of pneumococcal infection occurring in those children who were receiving penicillin (John 1984). Accordingly, most advisory health committees recommend early diagnosis of sickle cell disease in order that penicillin prophylaxis can be commenced in infancy (Lees 2000). The PROPS II trial

The PROPS II trial (PROPS II 1995) followed on from the first PROPS trial (PROPS 1986) to answer another important clinical question: if penicillin prophylaxis is to be given routinely to children with sickle cell disease, when is it safe to stop? The trial authors randomised SS and Sβ0Thal children to withdrawal or continuation of penicillin prophylaxis at five years of age, as previous studies have shown that the risk of infection is lower in older pre-school children (Zarkowsky 1986). Findings in the PROPS trial showed a risk of pneumococcal infection of 1.5 per 100 patient years in those receiving penicillin, and 9.8 per 100 patient years in the placebo group (PROPS 1986). In contrast, rates were significantly less in the PROPS II trial, with only 0.67 per 100 patient years in the placebo group, and half that in the penicillin group (PROPS II 1995). Thus rates of infection after the age of five years are shown to be lower, whether or not the child receives penicillin, and therefore children with sickle cell anemia who have neither had a prior severe pneumococcal infection or a splenectomy and are receiving comprehensive care may safely stop prophylactic penicillin therapy at 5 years of age (PROPS II 1995). without a clinically important increase in the risk of infection. For comparison, rates of invasive pneumococcal infection in the general non-sickle population in the USA are 0.0232 per 100 patient years, and 0.0352 per 100 patient years in the two to four year age group, dropping to 0.0039 after the age of five years (Robinson 2001). In the trial by John, penicillin was stopped at three years of age (John 1984). A cluster of four cases of pneumococcal infections occurred within 11 months of this, perhaps suggesting that these children are still very susceptible to infection, and that penicillin should be continued until they are older.

Adverse effects reported in the included trials were minimal. Compliance with the daily oral penicillin regimen is, however, known to be poor (Berkovitch 1998). The PROPS trial attempted to quantify the levels of compliance through pill counts and urine analysis, but too few data were collected for any conclusions to be drawn (PROPS 1986). Monthly intramuscular injections of penicillin overcome the problem of not taking pills, but require regular monthly interactions with the healthcare system. A lack of compliance with keeping these appointments is a real problem, particularly in rural, under-resourced areas. Additionally, the pain caused by intramuscular injections may not be acceptable to older children (John 1984). Also, there is some uncertainty regarding the efficacy of the depot preparations in the second half of the four-week period (Ginsburg 1982), although this did not seem to present a clinical problem in the included trial (John 1984).

Increasingly, the concern of antibiotic resistance is an issue for long-term antibiotic use. Infective organisms, which are resistant to antibiotics, are a growing problem in all areas of health care, and, although the impact of prophylactic antibiotic therapy on resistance is controversial (Anglin 1984), in general prolonged antimicrobial therapy is not encouraged (Pai 2000). In the PROPS II trial resistant organisms were isolated (PROPS II 1995). Observational studies have also shown a high level of colonization of resistant organisms (Daw 1997). In practice, the risks of pneumococcal infection to the individual should be balanced against the problem of resistant organisms to the population.

Overall completeness and applicability of evidence

The results of the trial by John show that a prophylactic penicillin regimen is also feasible in resource-limited countries (John 1984). The cost is variable but this has been quoted at a median cost of USD 0.31 for 2.4 million IU vials of powdered benzathine benzylpenicillin in a 2010 report from the United Nations Children's Fund (Wyber 2013). Also, monthly injections may aid compliance, providing individuals attend clinics regularly. The practicalities of implementing such a program in very rural and remote or under-resourced areas were illustrated in the trial, as several participants had to be moved from the penicillin groups due to inability to reach a medical centre every month. Children in different countries are exposed to different environmental factors, viral/bacterial risks and access to other medicines. This must be borne in mind when applying results of trials to difference settings.

Quality of the evidence

Three studies were eligible for inclusion, with sample sizes ranging from 215 to 400 children (John 1984; PROPS 1986; PROPS II 1995). The findings of the first PROPS trial was not in conflict with, but supported the results of, the John trial (John 1984; PROPS 1986). Of note, the route of administration for both trials differed, in the earlier trial the parenteral route was chosen, while in the latter trial penicillin was given orally. Additionally, during the John trial, which was five years in duration, penicillin was terminated after

each child's third birthday. This may have been a limitation of this trial. It was, however, noted that for the period of administration of intramuscular penicillin, children on this arm of the study had no pneumococcal infections. The quality of the evidence for both primary and secondary outcomes were judged to be low, see summary of findings tables (Summary of findings for the main comparison; Summary of findings 2).

The trial reports of the first PROPS trial provided a rigorous risk of bias assessment and all risk of bias domains could be adequately assessed. The risk of bias assessment showed that in regards to the other two studies (John 1984; PROPS 1986) ,there were some domains which were unclear, mainly due to inadequate reporting of the methods of randomization and allocation concealment and also in the reporting of outcome data (Figure 1; Figure 2). A high risk of bias as a result of allocation concealment (one of three studies) and incomplete outcome (one of three studies) was also reported. The existence of other sources of bias apart from those discussed and illustrated was not proven during the conduct of this review.

Potential biases in the review process

It is known that there was potential for bias to be introduced into the review and one of the ways the authors sought to reduce bias, as a result of study selection, was to have clear inclusion criteria to guide the extensive search strategy which was undertaken, This extensive search with suitable terminology increased the likelihood that all relevant studies were identified,

The methods used in assessing the risk of bias was one of the strengths of this review. The Cochrane risk of bias assessment tool provided a clear and uniform protocol for a rigorous 'risk of bias' assessment. Additionally, a two author review of the risk of bias allowed for greater reliability of this assessment.

One limitation of this review is that limitations in the reporting of the methodology did not allow complete risk of bias assessment for all studies. Where possible, the review authors tried to contact trial authors for clarifications, which assisted in the process and reduced the instances of an unclear assessment.

Agreements and disagreements with other studies or reviews

In the included trials, the efficacy of pneumococcal vaccines in children with SCD was questioned. A Cochrane Review has been undertaken to investigate pneumococcal vaccines in sickle cell disease (Davies 2004). For polysaccharide vaccines, two included trials found no evidence that incidence of pneumococcal infection was reduced in young children (under three years old) receiving the vaccine, but they were associated with increased minor adverse reactions. For the more recently introduced conjugate pneumococcal vaccines, there was evidence from three trials of an increased immune response, but no trials were identified which investigated the incidence of pneumococcal infections in children specifically with sickle cell disease (Davies 2004). However, trials undertaken in healthy children and children with HIV did demonstrate a significant decrease in risk (Black 2000; Klugman 2003). Such recent improvements in pneumococcal vaccines may reduce the requirement for antibiotic prophylaxis.

AUTHORS' CONCLUSIONS

Implications for practice

Penicillin prophylaxis reduces the incidence of pneumococcal infections in children with sickle cell disease (SS or Sβ0Thal) under the age of five years. The risk of infection in children older than five years is lower, and the PROPS II trial did not show a significant increase in the risk on withdrawal of prophylactic penicillin at this age.

Implications for research

Observational data may help to elucidate the risk of infection in children when penicillin prophylaxis is withdrawn. In addition, further research into prevalence and clinical importance of resistant organisms is needed.

ACKNOWLEDGEMENTS

This project was supported by the National Institute for Health Research, via Cochrane Infrastructure funding to the Cochrane Cystic Fibrosis and Genetic Disorders Group. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS or the Department of Health.

REFERENCES

References to studies included in this review

John 1984 *{published data only}*

John AB, Ramlal A, Jackson H, Maude GH, Sharma AW, Serjeant GR. Prevention of pneumococcal infection in children with homozygous sickle cell disease. *British Medical Journal (Clinical Research Edition)* 1984;**288**(6430):1567-70.

PROPS 1986 *{published data only}*

Gaston MH, Verter J. Sickle cell anaemia trial. *Statistics in Medicine* 1990;**9**(1-2):45-51.

* Gaston MH, Verter JI, Woods G, Pegelow C, Kelleher J, Presbury G, et al. Prophylaxis with oral penicillin in children with sickle cell anemia: a randomized trial. *New England Journal of Medicine* 1986;**314**(25):1593-9.

PROPS II 1995 *{published data only}*

Bjornson AB, Falletta JM, Verter JI, Buchanan GR, Miller ST, Pegelow CH, et al. Serotype-specific immunoglobulin G antibody responses to pneumococcal vaccine in children with sickle cell anemia: effects of continued penicillin prophylaxis. *Journal of Pediatrics* 1996;**129**(6):828-35.

Falletta JM, Woods GM, Verter JI, Buchanan GR, Pegelow CH, Iyer RV, et al. Discontinuing penicillin prophylaxis in children with sickle cell anemia. Prophylactic Penicillin Study II. *Journal of Pediatrics* 1995;**127**(5):685-90.

Woods GM, Jorgensen JH, Waclawiw MA, Reid C, Wang W, Pegelow CH, et al. Influence of penicillin prophylaxis on antimicrobial resistance in nasopharyngeal S. pneumoniae among children with sickle cell anemia. The Ancillary Nasopharyngeal Culture Study of Prophylactic Penicillin Study II. *Journal of Pediatric Hematology/Oncology* 1997;**19**(4):327-33.

References to studies excluded from this review

Berkovitch 1998 *{published data only}*

Berkovitch M, Papadouris D, Shaw D, Onuaha N, Dias C, Olivieri NF. Trying to improve compliance with prophylactic penicillin therapy in children with sickle cell disease. *British Journal of Clinical Pharmacology* 1998;**45**(6):605-7.

Lewthwaite 1962 *{published data only}*

Lewthwaite CJ. A trial of chemoprophylaxis in sickle cell anaemia. Preliminary communication.. *East African Medical Journal* 1962;**39**(5):196-9.

Additional references

Anglin 1984

Anglin DL, Siegel JD, Pacini DL, Smith SJ, Adams G, Buchanan G. Effect of penicillin prophylaxis on nasopharyngeal colonization with Streptococcus pneumoniae in children with sickle cell anemia. *Journal of Pediatrics* 1984;**104**(1):18-22.

Black 2000

Black S, Shinefield H, Fireman B, Lewis P, Ray P, Hansen JR, et al. Efficacy, safety and immunogenicity of hepavalent pneumococcal conjugated vaccine in children. Northern California Kaiser Permanente Vaccine Study Center Group. *Pediatric Infectious Disease Journal* 2000;**19**(3):187-95.

BNF 2001

British Medical Association, Royal Pharmaceutical Society of Great Britain. British National Formulary. 42. London: BMJ Books, 2001.

Chesney 1992

Chesney PJ. The escalating problem of antimicrobial resistance in Streptococcus pneumoniae. *American Journal of Diseases of Children* 1992;**146**(8):912-6.

Cummins 1991

Cummins D, Heuschkel R, Davies SC. Penicillin prophylaxis in children with sickle cell disease in Brent. *BMJ* 1991;**302**(6783):989-90.

Davies 1997

Davies SC, Oni L. The management of patients with sickle cell disease. *BMJ* 1997;**315**(7109):656-60.

Davies 2004

Davies GE, Hirst C, Lottenberg R, Dower N. Pneumococcal vaccines for sickle cell disease (Cochrane Review). *Cochrane Database of Systematic Reviews* 2004, Issue 1. [DOI: 10.1002/14651858.CD003885.pub2]

Daw 1997

Daw NC, Wilimas JA, Wang WC, Presbury GJ, Joyner RE, Harris SC, et al. Nasopharyngeal carriage of penicillin resistant Streptococcus Pneumoniae in children with sickle cell disease. *Pediatrics* 1997;**99**(4):E7.

Ginsburg 1982

Ginsburg CM, McCracken GH, Zweighaft TC. Serum penicillin concentrations after intramuscular administration of benzathine penicillin G in children. *Pediatrics* 1982;**69**(4):452-4.

Hickman 1999

Hickman M, Modell B, Greengross P, Chapman C, Layton M, Falconer S, et al. Mapping the prevalence of sickle cell and beta thalassaemia in England: estimating and validating ethnic-specific rates. *British Journal of Haematology* 1999;**104**(4):860-7.

Higgins 2003

Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**(7414):557-60.

Higgins 2011

Higgins 2011: Higgins JPT, Altman DG, Sterne JAC, editor (s). Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0 (updated March

2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Klugman 2003

Klugman KP, Madhi SA, Huebner RE, Kohberger R, Mbelle N, Pierce N, et al. A trial of 9-valent pneumococcal conjugate vaccine in children with and those without HIV infection. *New England Journal of Medicine* 2003;**349**(14):1341-8.

Lee 1995

Lee A, Thomas P, Cupidore L, Serjeant B, Serjeant G. Improved survival in homozygous sickle cell disease: lessons from a cohort study. *BMJ* 1995;**311**(7020):1600-2.

Lees 2000

Lees CM, Davies S, Dezateux C. Neonatal screening for sickle cell disease (Cochrane Review). *Cochrane Database of Systematic Reviews* 2000, Issue 1. [DOI: 10.1002/14651858.CD001913]

Leikin 1989

Leikin SL, Gallagher D, Kinney TR, Sloane D, Klug P, Rida W. Mortality in children and adolescents with sickle cell disease. Co-operative Study of Sickle Cell Disease. *Pediatrics* 1989;**84**(3):500-8.

Lobel 1982

Lobel JS, Bove KE. Clinicopathologic characteristics of septicaemia in sickle cell disease. *American Journal of Diseases of Children* 1982;**136**(6):543-7.

Pai 2000

Pai VB, Nahata MC. Duration of penicillin prophylaxis in sickle cell anemia: issues and controversies. *Pharmacotherapy* 2000;**20**(1):110-7.

Platt 1994

Platt OS, Brambilla DJ, Rosse WF, Milner PF, Castro O, Steinberg MH, et al. Mortality in sickle cell disease: life expectancy and risk factors for early death. *New England Journal of Medicine* 1994;**330**(23):1639-44.

Robinson 1966

Robinson MG, Watson RJ. Pneumococcal meningitis in sickle-cell anemia. *The New England Journal of Medicine* 1966;**274**(18):1006-8.

Robinson 2001

Robinson KA, Baughman W, Rothrock G, Barrett NL, Pass M, Lexau C, et al. Epidemiology of invasive Streptococcus pneumoniae infections in the United States, 1995-1998. Opportunities for prevention in the conjugate vaccine era.. *JAMA* 2001;**285**(13):1729-35.

Serjeant 2001

Serjeant GR, Serjeant BE. The immune system. Sickle Cell Disease. 3rd Edition. Oxford University Press, 2001:153-66.

Woods 1997

Woods GM, Jorgensen JH, Waclawiw MA, Reid C, Wang W, Pegelow CH, et al. Influence of penicillin prophylaxis on antimicrobial resistance in nasopharyngeal S. pneumoniae among children with sickle cell anemia. The Ancillary Nasopharyngeal Culture Study of Prophylactic Penicillin Study II. *Journal of Pediatric Hematology/Oncology* 1997;**19**(4):327-33.

Wyber 2013

Wyber R, Taubert K, Marko S, Kaplan E. Benzathine Penicillin G for the Management of RHD: Concerns About Quality and Access, and Opportunities for Intervention and Improvement. *Global Heart* 2013;**8**(3):227-34.

Zarkowsky 1986

Zarkowsky HS, Gallagher D, Gill FM, Wang WC, Falletta JM, Lande WM, et al. Bacteremia in sickle hemoglobinopathies. *Journal of Pediatrics* 1986;**109**(4):579-85.

References to other published versions of this review

Hirst 2002

Hirst C, Owusu-Ofori S. Prophylactic antibiotics for preventing pneumococcal infection in children with sickle cell disease. *Cochrane Database of Systematic Reviews* 2002, Issue 3. [DOI: 10.1002/14651858.CD003427]

Hirst 2012

Hirst C, Owusu-Ofori S. Prophylactic antibiotics for preventing pneumococcal infection in children with sickle cell disease. *Cochrane Database of Systematic Reviews* 2012, Issue 9. [DOI: 10.1002/14651858.CD003427.pub2]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

John 1984

Methods	Participants randomised to penicillin prophylaxis or no treatment, together with 1 of 2 vaccines. No details of randomisation given.
Participants	265 randomised, but 23 of these were subsequently withdrawn, mostly due to revision of genotype, leaving a total of 242 children with SS in Jamaica, West Indies. Trial duration: 5 years

John 1984 *(Continued)*

Interventions	Penicillin monthly IM injection, pneumococcal vaccine, *H influenzae* type B vaccine.
Outcomes	Incidence of pneumococcal infection (isolated).
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"A total of 265 children were randomised to the four study groups." no details were given of the method of randomization we are therefore unable to fully assess the risk of selection bias.
Allocation concealment (selection bias)	High risk	"A revision of protocol withholding penicillin was necessary for 16 patients, eight of whom lived at remote addresses and eight of whom entered between 31 and 35 months of age, which would have resulted in too short a treatment period to assess efficacy. These 16 were assigned to the corresponding vaccine groups without penicillin."
Blinding (performance bias and detection bias) All outcomes	Low risk	Trial not blinded; however, the primary study outcome (number of participants developing *Streptococcus pneumoniae* infection confirmed with cultures or number of deaths as a result of such an infection) and the secondary study outcome (adverse drug reaction) are not affected by the fact that blinding did not take place.
Incomplete outcome data (attrition bias) All outcomes	High risk	A total of 265 children were randomised to the four study groups, but 23 of these were subsequently withdrawn, mostly due to revision of genotype. "The trial was terminated prematurely in 25 children owing to splenectomy in 20, emigration in four, and the clinical decision to use prophylactic penicillin in one child with recurrent pneumococcal meningitis In these cases results up to the time of leaving the study were included in the analysis. There were seven deviations from the protocol caused by refusal to take penicillin after two and four injections (two), death before institution of randomised treatment (one), failure to treat with penicillin because of an error in age (one), inadvertent administration of penicillin to patients joining the study between 31 and 35 months of age (two), and removal to an inaccessible address, so that penicillin had to be stopped (one)." Aditionally, the study groups were also uneven with more participants in the penicillin group (143 in the penicillin group compared to 90 in the control group) and an "Intention to treat analysis was also undertaken" after participants were reassigned to protocol groups.
Selective Reporting (Reporting Bias)	Low risk	"The pneumococcal prevention study began in May 1978. A 2x2 factorial design was used to compare (a) the response to pneumococcal vaccine with that to Haemophilus influenzae type B vaccine as a capsular polysaccharide antigen control and (b) the effect of penicillin with that of no penicillin." All outcomes were satisfactorily reported.
Other potential Sources of Bias	Low risk	None known.

PROPS 1986

Methods	Participants randomised to penicillin prophylaxis or placebo by central blocked randomisation.

PROPS 1986 *(Continued)*

Participants	215 children with SS in USA.
Interventions	Penicillin V (125 mg twice daily, oral), or placebo (vitamin C 50 mg twice daily). Trial terminated 8 months early after an average of 15 months follow up.
Outcomes	Documented bacterial infection (i) *S pneumoniae* (ii) any other organism.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The PROPS data coordinating center generated the randomization numbers for each clinical site and with the help of the program office, directed patient - entry assignments by means of telephone contact. Sealed envelopes that were stored at the clinical centres were available as a back up for randomization when telephone contact was not possible, but they were rarely used. The randomization schedules were prepared with the use of blocked randomization within each clinic to ensure balance in numbers between two groups."
Allocation concealment (selection bias)	Low risk	A central co-ordinating centre directed participant entry assignment over the telephone. Sealed envelopes were also held at the clinical centres in case the central office could not be reached, to maintain allocation concealment.
Blinding (performance bias and detection bias) All outcomes	Low risk	The participants and centre personnel were blinded to allocation, and placebo tablets looked almost identical to penicillin.
Incomplete outcome data (attrition bias) All outcomes	High risk	219 participants were recruited from 23 centres throughout the USA. Four participants subsequently withdrew due to revisions of diagnosis of genotype; these patients had no severe infections but were not included in subsequent analyses. The baseline characteristics of the children in each group, including history of palpable spleen or infection, were similar. The trial was terminated early due to extreme results. Because of this, there is a possibility that the reported results may be over-estimated.
Selective Reporting (Reporting Bias)	Low risk	Both the primary and secondary outcomes were adequately reported "the trial was terminated earlier ....., after the occurrence of 15 episodes of pneumococcal sepsis 13 in the placebo group and 2 in the penicillin group". Additionally baseline characteristics of both study groups are adequately reported.
Other potential Sources of Bias	Low risk	None known.

PROPS II 1995

Methods	Participants randomised to have prophylactic penicillin withdrawn or continued, by permuted block randomisation.
Participants	400 children with SS or Sb0 in USA.
Interventions	Penicillin V (250 mg twice daily), or identical placebo tablet.
Outcomes	Incidence of bacteremia or meningitis caused by *S pneumoniae*.

PROPS II 1995 *(Continued)*

	Average duration of follow-up: 3.2 years.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was by permuted block method, stratified by clinical site and years of previous penicillin use.
Allocation concealment (selection bias)	Unclear risk	It was unclear whether allocation concealment had been performed.
Blinding (performance bias and detection bias) All outcomes	Low risk	Identical placebo tablets were used to maintain double blinding of the participants and centre personnel.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	400 participants were recruited from 18 centres in the USA. The characteristics of participants in each group were similar at baseline. Four children died after randomisation, but other withdrawals are not reported, and it is unclear whether an intention-to-treat analysis was undertaken.
Selective Reporting (Reporting Bias)	Low risk	"The primary end point was a comparison of the incidence of bacteremia or meningitis caused by Streptococcus pneumoniae in children continuing penicillin prophylaxis versus those receiving the placebo." Baseline characteristics and outcomes were adequately reported
Other potential Sources of Bias	Low risk	None known.

bd: twice daily
H influenzae: *Haemophilus influenzae*
IM: intramuscular
S pneumoniae: *Streptococcus pneumoniae*
SS: homozygous sickle cell disease

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Berkovitch 1998	All participants received penicillin and were randomised to a 'compliance aid' or not.
Lewthwaite 1962	Alternate cases attending an outpatient clinic were given a SC injection of chloroquine and an IM injection of penicillin. The control group received a SC injection of sterile water. Randomisation process was inadequate, of the 26 participants recruited only 13 were accounted for, outcomes were unclear and there was no mention of *S pneumoniae*.

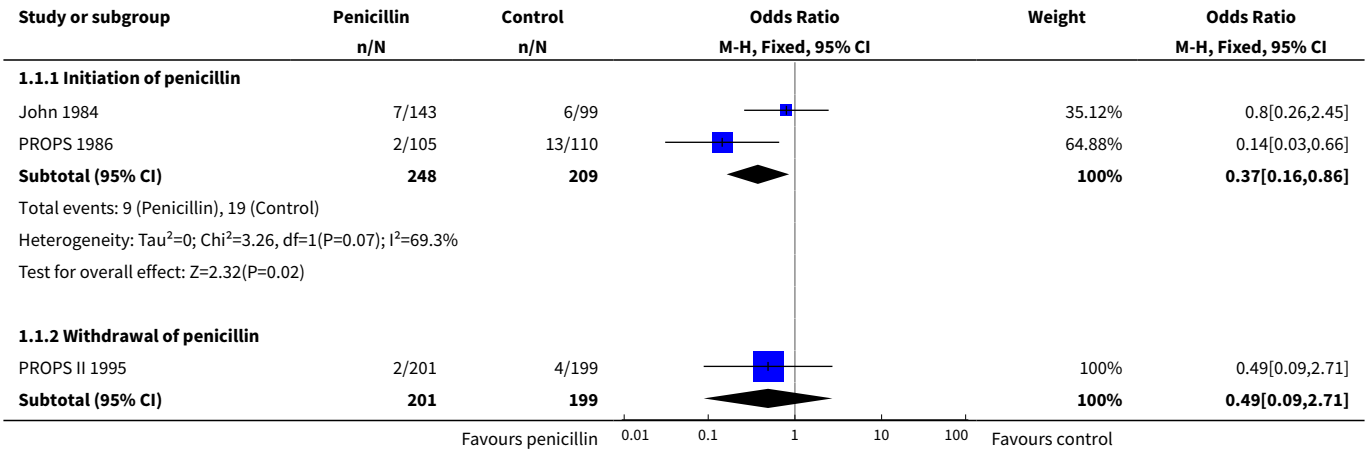
IM: intramuscular
SC: subcutaneous
S pneumoniae: *Streptococcus pneumoniae*

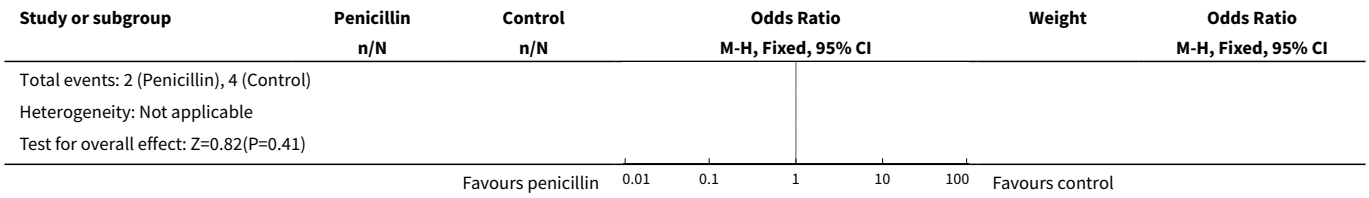
DATA AND ANALYSES

Comparison 1. Penicillin prophylaxis versus standard care

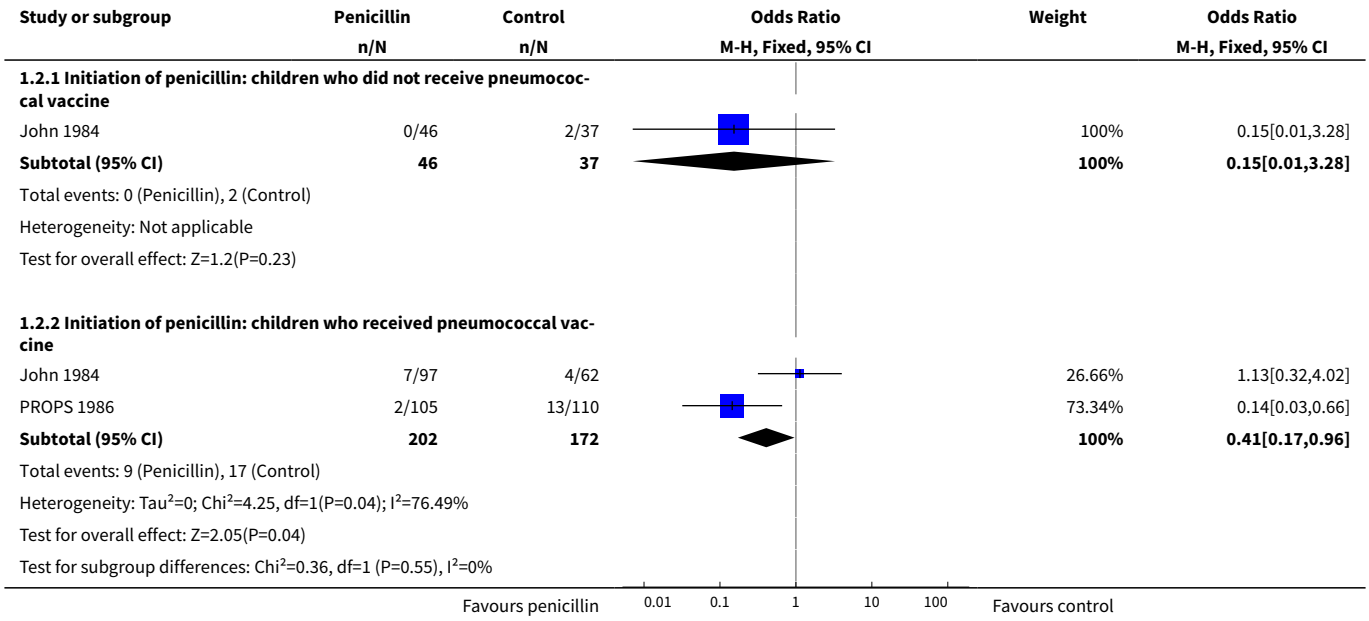
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Incidence of pneumococcal infection, for initiation or withdrawal of treatment	3		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Initiation of penicillin	2	457	Odds Ratio (M-H, Fixed, 95% CI)	0.37 [0.16, 0.86]
1.2 Withdrawal of penicillin	1	400	Odds Ratio (M-H, Fixed, 95% CI)	0.49 [0.09, 2.71]
2 Incidence of pneumococcal infection, subgrouped by vaccination	2		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Initiation of penicillin: children who did not receive pneumococcal vaccine	1	83	Odds Ratio (M-H, Fixed, 95% CI)	0.15 [0.01, 3.28]
2.2 Initiation of penicillin: children who received pneumococcal vaccine	2	374	Odds Ratio (M-H, Fixed, 95% CI)	0.41 [0.17, 0.96]
3 Deaths, for initiation or withdrawal of treatment	3		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Initiation of penicillin	2	457	Odds Ratio (M-H, Fixed, 95% CI)	0.11 [0.01, 2.11]
3.2 Withdrawal of penicillin	1	400	Odds Ratio (M-H, Fixed, 95% CI)	0.99 [0.14, 7.10]
4 Adverse drug effects	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.1 Nausea and vomiting	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Requirement for other courses of antibiotics	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only

Analysis 1.1. Comparison 1 Penicillin prophylaxis versus standard care, Outcome 1 Incidence of pneumococcal infection, for initiation or withdrawal of treatment.

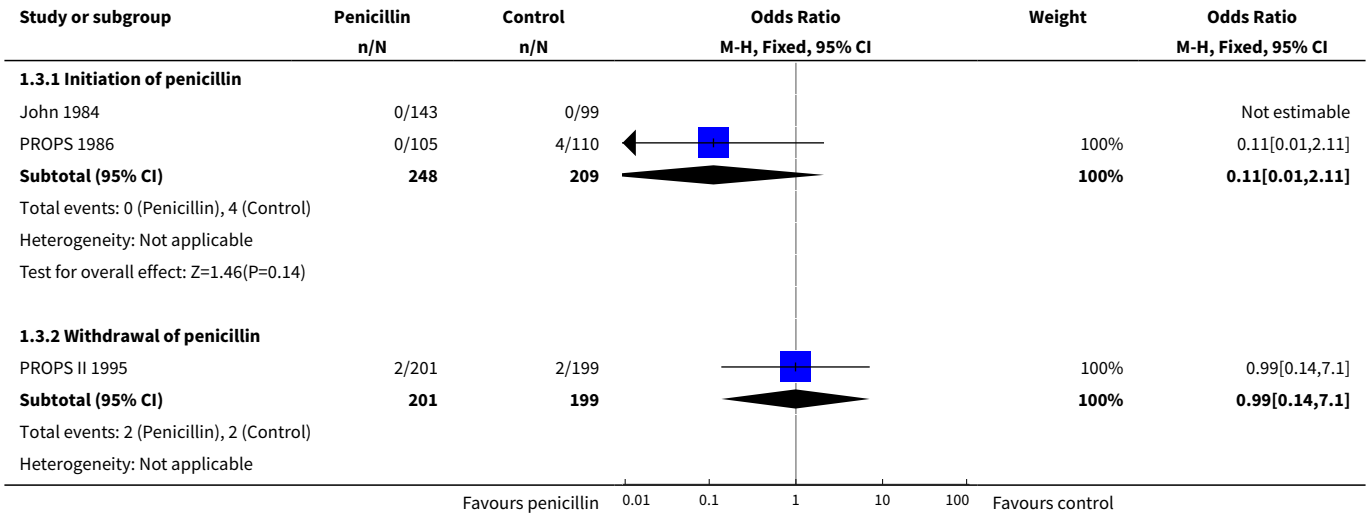




Analysis 1.2. Comparison 1 Penicillin prophylaxis versus standard care, Outcome 2 Incidence of pneumococcal infection, subgrouped by vaccination.



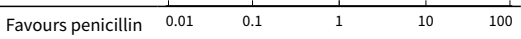
Analysis 1.3. Comparison 1 Penicillin prophylaxis versus standard care, Outcome 3 Deaths, for initiation or withdrawal of treatment.



Study or subgroup	Penicillin n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Test for overall effect: Z=0.01(P=0.99)					

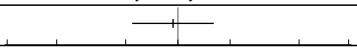
Analysis 1.4. Comparison 1 Penicillin prophylaxis versus standard care, Outcome 4 Adverse drug effects.

Study or subgroup	Penicillin n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
1.4.1 Nausea and vomiting				
PROPS II 1995	2/201	1/199		1.99[0.18,22.12]



Analysis 1.5. Comparison 1 Penicillin prophylaxis versus standard care, Outcome 5 Requirement for other courses of antibiotics.

Study or subgroup	Penicillin n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
PROPS II 1995	169/201	169/199		0%	0.94[0.55,1.61]



APPENDICES

Appendix 1. Search strategies

Database/Resource	Strategy
www.Clinicaltrials.gov	[ADVANCED SEARCH] SEARCH TERMS: pneumococcal OR pneumococcus OR Streptococcus OR Streptococcal OR Pneumoniae OR pneumonia STUDY TYPE: interventional Studies CONDITIONS: sickle
WHO International Clinical Trials Registry Platform (ICTRP)	Three separate searches were carried out: SEARCH 1: sickle AND pneumococcus SEARCH 2: sickle AND Streptococcus SEARCH 3: sickle AND Pneumococcus

WHAT'S NEW

Date	Event	Description
5 March 2020	Amended	The previous lead author (Ceri Hirst) was conflicted for the 2009, 2012, 2015 versions of this review. Clarification reflecting this has been added to 'Published notes'.

HISTORY

Protocol first published: Issue 1, 2002
Review first published: Issue 3, 2002

Date	Event	Description
2 October 2017	New search has been performed	A new lead author (Angela Rankine-Mullings) has produced this update, along with the previous co-author (Shirley Owusu-Ofori). Searches of the Cochrane Cystic Fibrosis and Genetic Disorders Haemoglobinopathies Trials Register, Clinicaltrials.gov and the WHO International Registry Platform did not identify any potentially relevant trials.
2 October 2017	New citation required but conclusions have not changed	The text has been updated throughout the review. The assessment of the risk of bias was significantly updated. Summary of findings tables have been added and incorporated into all sections of the review. The conclusions have not changed.
11 February 2015	Amended	Contact details updated.
3 July 2014	New citation required but conclusions have not changed	Minor changes to the text have been made throughout the review.
3 July 2014	New search has been performed	A search of the Cystic Fibrosis and Genetic Disorders Trials Register did not identify any potentially relevant trials for inclusion in the review update.
14 June 2012	New search has been performed	A search of the Group's Haemoglobiopathies Trials Register did not identify and potentially eligible trials.
14 June 2012	New citation required but conclusions have not changed	The review was updated but no major changes were made.
20 September 2010	Amended	Contact details updated.
16 April 2010	New search has been performed	A search of the Group's Haemoglobinopathies Trials Register identified no additional trials potentially eligible for inclusion in this review.
12 August 2009	Amended	Contact details updated.
23 October 2008	New search has been performed	The search of the Group's Haemoglobinopathies Trials Register did not identify any potentially eligible trials for inclusion in the review.
1 October 2008	Amended	Converted to new review format.

Date	Event	Description
1 August 2007	New search has been performed	A search of the Group's Haemoglobinopathies Trials Register identified no additional trials eligible for inclusion in this review.
1 August 2007	Amended	The 'Synopsis' has been replaced by a new 'Plain language summary'.
1 August 2006	New search has been performed	A search of the Group's Haemoglobinopathies Trials Register identified no additional trials eligible for inclusion in this review.
1 April 2005	New search has been performed	A search of the Group's Haemoglobinopathies Trials Register identified no additional trials eligible for inclusion in this review. The lead author has changed her family name from Riddington to Hirst.
1 March 2004	New search has been performed	A search of the Group's trials register identified no additional trials eligible for inclusion in this review.
1 March 2003	New search has been performed	An additional reference (Bjornson 1996) to an already included study (PROPS II 1995) has been added. There is no new evidence to add from this reference. An additional reference (Gaston 1990) to an already included study (PROPS 1986) has been added. There is no new evidence to add from this reference. The review has been updated with additional information from authors: Less than 10% of participants were involved in both of the following studies: PROPS 1986 and PROPS II 1995.

CONTRIBUTIONS OF AUTHORS

Current version of the review

Dr Angela Rankine-Mullings lead on the 2017 update of this review and acts as guarantor.
Dr Owusu-Ofori commented on the final draft version.

For previous versions of the review

The review was conceived by the Cochrane Cystic Fibrosis and Genetic Disorders Group and designed by Dr Hirst (née Riddington) and Dr Owusu-Ofori.

The authors and the Cochrane Cystic Fibrosis and Genetic Disorders Group conducted searches for relevant studies.

The same two authors screened, appraised and abstracted data for the review. Dr Hirst sought additional information from authors where necessary. Data entry was performed and interpreted by Dr Hirst and Dr Owusu-Ofori with advice from the Cochrane Cystic Fibrosis and Genetic Disorders Group.

Dr Hirst and Dr Owusu-Ofori completed the updates of the review.

Dr Hirst acts as guarantor for the review.

DECLARATIONS OF INTEREST

Both authors: none known.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- National Institute for Health Research, UK.

This systematic review was supported by the National Institute for Health Research, via Cochrane Infrastructure funding to the Cochrane Cystic Fibrosis and Genetic Disorders Group.

NOTES

The previous lead author (Ceri Hirst) was conflicted for the 2009, 2012, 2015 versions of this review. This was due to employment at AstraZeneca and Roche during this period.

INDEX TERMS

Medical Subject Headings (MeSH)

*Antibiotic Prophylaxis [adverse effects]; Age Factors; Anemia, Sickle Cell [*complications] [genetics]; Hemoglobin SC Disease [complications]; Homozygote; Incidence; Penicillins [adverse effects] [*therapeutic use]; Pneumococcal Infections [epidemiology] [*prevention & control]; Randomized Controlled Trials as Topic; beta-Thalassemia [complications]

MeSH check words

Child, Preschool; Humans; Infant